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Review

Molecular mechanisms of bone formation in spondyloarthritis

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ABSTRACT

Spondyloarthritis comprise a group of inflammatory rheumatic diseases characterized by its association to HLA-B27 and the presence of arthritis and enthesitis. The pathogenesis involves both an inflammatory process and new bone formation, which eventually lead to ankylosis of the spine. To date, the intrinsic mechanisms of the pathogenic process have not been fully elucidated, and our progress is remarkable in the identification of therapeutic targets to achieve the control of the inflammatory process, yet our ability to inhibit the excessive bone formation is still insufficient. The study of new bone formation in spondyloarthritis has been mostly conducted in animal models of the disease and only few experiments have been done using human biopsies. The deregulation and overexpression of molecules involved in the osteogenesis process have been observed in bone cells, mesenchymal cells, and fibroblasts. The signaling associated to the excessive bone formation is congruent with those involved in the physiological processes of bone remodeling. Bone morphogenetic proteins and Wnt pathways have been found deregulated in this disease; however, the cause for uncontrolled stimulation remains unknown. Mechanical stress appears to play an important role in the pathological osteogenesis process; nevertheless, the association of other important factors, such as the presence of HLA-B27 and environmental factors, remains uncertain. The present review summarizes the experimental findings that describe the signaling pathways involved in the new bone formation process in spondyloarthritis in animal models and in human biopsies. The role of mechanical stress as the trigger of these pathways is also reviewed.

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1. Introduction

Spondyloarthritis (SpA) are an interrelated group of rheumatic diseases characterized by common clinical symptoms and genetic similarities. The most important clinical features include inflammatory back pain, asymmetric peripheral oligoarthritis, predominantly in lower limbs, enthesitis, and sacroiliitis. The SpA may also involve specific organs, such as in anterior uveitis, psoriasis and chronic inflammatory bowel disease [1]. Ankylosing spondylitis (AS) is the prototype disease in the study of SpA and its hallmark is the new bone formation at sites of enthesitis [2].

All SpA subtypes, including AS, psoriatic arthritis, enteropathic arthritis, reactive arthritis, juvenile SpA and undifferentiated SpA, are characterized by arthritis and enthesitis although their location, severity and pattern varies. Particularly in AS, new bone formation leading to bone fusion (ankylosis) of sacroiliac joints as well as syndesmophytes that bridge the edges of the vertebral bodies, or enthesophytes that proliferate from the edges of the entheses in axial and appendicular skeleton. For most SpA patients, the disease burden results from the combination of the bone inflammation and osteoproliferative structural changes. To date, the link between inflammation and bone proliferation processes remains elusive and a certain degree of independence between both processes has been proposed [3,4].

The new bone formation in SpA includes the proliferation of mesenchymal precursors, their commitment to the bone lineage and eventual maturation, and their migration and eventual cell death. The osteoproliferation in SpA is a complex process of tissue remodeling that shares similarities with joint remodeling in osteoarthritis [5]. The distinction between physiological and pathological process of bone formation is particularly clear in the SpA: whereas the new bone is formed in excess on the outer surface of cortical bone, paradoxically, SpA patients develop osteoporosis due to degradation of trabecular bone of the vertebral bodies. These types of divergent remodeling in cortical and trabecular bone in SpA patients suggest that pathological bone remodeling in SpA is clearly

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Table 1
Molecular mechanisms of new bone formation in SpA human samples.

Authors	Sample	Molecular pathway	Analyzed molecules	Analysis technique	Findings
Appel et al., 2010 [5]	Zygapophyseal joints of AS patients	Bone differentiation	OPG, RANKL, OCN	IHQ	Levels of OCN+, OPG+, and RANKL+ osteoblasts did not differ between AS and OA Levels of OPG+ and OC+ but not RANKL+ osteoblasts were significantly lower in controls compared to AS patients *Osteoblast activity is similar in AS and OA, indicating that new bone formation is possibly a physiological function of repair in both diseases*
Pacheco-Tena et al., 2014 [7]	Synovial sheaths, entheses, and bone samples of AT patients	Bone differentiation	OCN, OPN, PTHrP, BSP, ALP	IHQ, IF	OCN, OPN, BSP, and PTHrP were found in the entheseal and osteal tissues showing bone proliferation OCN and OPN are over expressed in ankylosis tarsitis biopsies compared with normal controls OCN and OPN are expressed in a fibroblast-mesenchymal phenotype cells *OCN and OPN in cells with a fibroblast-mesenchymal phenotype, suggesting the induction of entheseal cells toward an osteoblast phenotype*
Lories et al., 2005 [8]	Entheseal biopsies obtained from Achilles tendons of SpA patients	BMP/Smad	BMP-2, BMP-6, BMP-7, p-Smad 1/5/8, PCNA	IF	Positive phosphorylated smad1/5/8 proliferating cells and negative chondrocytes Co-localization of phosphorylated smad1/5/8 and PCNA Immunoreactivity for BMP2, BMP7, and BMP6 was recognized in proliferating spindle-shaped cells and in prehypertrophic and mature chondrocytes, respectively *Activation of BMP signaling in the proliferating and differentiating cell population by the presence of nuclear phosphorylated smad1/5*
Wang et al., 2012 [9]	Sacroiliac joint tissue samples of AS patients	TGF-β1/Smad	TGF-β1, p-Smad3, Smad7, CTGF, type I and III collagen	IHQ	TGF-β1 and CTGF were over expressed in cytoplasm of inflammatory cells in pannus and bone marrow Meantime, p-Smad3 was expressed in the nuclear, while Smad7 was down expressed Type I and III collagen were over expressed in bone, cartilage and ligament tissue *TGF-β1/CTGF may play an important role in articular cartilage fibrosis and ossification of AS by Smad signal pathway*
Joo et al., 2014 [10]	Blood	BMP	52 genes related to bone formation	SNPs	Identification of new loci of BMP-6 associated with radiographic severity in patients with AS Two SNPs in BMP6 (rs270378 and rs1235192) were significantly associated with radiologic severity *BMP6 is associated with radiographic severity in AS, supporting the role wingless-type like/BMP pathway on radiographic progression in AS*
Thomas et al., 2013 [11]	Knee synovial biopsies of AS/SpA patients	WNT	MMP3, Dkk-3, Kremen1	WGEP, qPCR, IHQ	Four hundred and sixteen differentially expressed genes were identified that clearly delineated between AS/SpA and control groups Pathway analysis showed altered gene expression in oxidoreductase activity, B-cell associated, matrix catabolic, and metabolic pathways Altered "myogene" profiling was also identified The inflammatory mediator, MMP3, was strongly upregulated in AS/SpA samples Wnt pathway inhibitors, DKK3 and Kremen1, were downregulated *Supports the hypothesis that initial systemic inflammation in SpA transfers to and persists in the local joint environment, and might subsequently mediate changes in genes directly involved in the destructive tissue remodelling*

ALP: alkaline phosphatase; AS: ankylosing spondylitis; AT: ankylosing tarsitis; BMP: bone morphogenetic protein; BSP: bone sialoprotein; CTGF: connective tissue growth factor; Dkk-3: dickkopf-related protein 3; IF: immunofluorescence; IHQ: immunohistochemistry; MMP3: matrix metalloproteinase 3; OA: Osteoarthritis; OCN: osteocalcin; OPG: osteoprotegerin; OPN: osteopontin; p-: phosphorylated-; PCNA: proliferating cell nuclear antigen; PTHrP: parathyroid hormone-related protein; qPCR: quantitative polymerase chain reaction; RANKL: nuclear factor-kappaB ligand; SNPs: single nucleotide polymorphisms; SpA: spondyloarthritis; TGF-β: transforming growth factor beta; WGEP: whole genome expression profiling. The main findings are highlighted in italics.

different from the classic bone turnover. Moreover, the inflammation control reverts the loss of trabecular bone, but does not seem to affect the cortical osteoproliferative ankylosing progression [6].

Studies of molecular mechanisms of new bone formation processes in humans with SpA are scarce (Table 1). Most of these are limited to histological findings suggesting a contribution from the endochondral and membranous bone formation in the development of ankylosis [5,12–15]. Recently our laboratory reports the osteoproliferation and abnormal expression of bone lineage proteins: osteocalcin, osteopontin, parathyroid hormone-related protein and bone sialoprotein in biopsies of the entheses of ankylosing tarsitis patients compared with normal biopsies. These results suggested that ossification process may be, in part, explained by the differentiation of mesenchymal entheseal cells toward the osteoblastic lineage [7]. Molecular mechanisms of new bone formation have been studied mainly in animal models of SpA [16]. The signaling pathways described in these models are consistent with the pathways involved in the normal process of bone formation, wherein the bone morphogenetic proteins (BMP), Wnt and Hedgehog (Hh) proteins have been the most involved. Interestingly, in the last decades, the influence of mechanical stress has been linked to the process of new bone formation in SpA, however, its direct association with specific signaling pathways remains unclear.

2. Bone morphogenetic proteins signaling pathways in SpA

The BMPs are morphogenic growth factors and cytokines, which were originally identified as proteins able to induce the full cascade of endochondral bone formation [17,18]. Currently BMPs are recognized as members of the superfamily of transforming growth factor beta (TGF-β) [19]. In the essential process of endochondral ossification, the mesenchymal progenitor cells differentiate into

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